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Health-related quality of life 10 years after oesophageal cancer surgery

Running head: Long-term quality of life and oesophageal cancer

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Abstract

Purpose: To determine whether oesophageal cancer survivors recover in health-related quality of life (HRQOL) within 10 years of surgery.

Methods: A prospective, nationwide, population-based cohort study including 90% of all oesophageal cancer surgery patients in Sweden in 2001-2005, with follow-up through 2015. HRQOL was assessed 5 and 10 years postoperatively, using questionnaires for cancer in general (EORTC QLQ-C30) and oesophageal cancer specifically (EORTC QLQ-OES18). The HRQOL measures at 10 years after surgery were compared with the 5 year assessment. The 10-year HRQOL scores were compared with a population-based reference population (4,910 individuals), individually matched for age, sex, and comorbidity, by means of mean score differences with 95% confidence intervals.

Results: Among 616 patients, 104 (17%) survived at least 10 years. Of these, 92 (88%) responded to the HRQOL questionnaires at 5 and 10 years after surgery. Among the responders, 71% were older than 70 years. Patients did not improve in HRQOL between 5 and 10 years. Instead, the scores for 23 out of 25 HRQOL aspects declined, with clinically relevant and statistically significant deterioration in role function and appetite loss. Compared to the reference population, the 10 year survivors had worse scores in all 25 HRQOL aspects, with significant deterioration in global quality of life, role functioning, social functioning, and most symptoms. The most severe problems compared to the reference population were reflux, eating difficulties, diarrhoea, and appetite loss.

Conclusion: Patients who have undergone curative treatment for oesophageal cancer experience reduced HRQOL with persisting symptoms 10 years after surgery.

Background

With an age-adjusted incidence rate of 4.3 per 100,000 persons,[1] oesophageal cancer is the 8th most common cancer globally.[2] The prognosis is poor (<20% 5-year survival) because of late symptom presentation and early metastatic spread.[2,3] The dominant curatively intended treatment involves surgical resection, often in combination with neoadjuvant chemotherapy or chemoradiotherapy.[4] The surgery is extraordinarily extensive and entails >40% risk of postoperative complications[5,6] and a 5-year survival of 40% for patients without metastatic spread.[1] The postoperative recovery is typically slow with long-lasting impairments in health-related quality of life (HRQOL).[7,8] HRQOL is greatly affected immediately after surgery, and although some patients regain their preoperative HRQOL within the first year of surgery,[9] several symptoms may persist.[10,11] Importantly, a significant subgroup of patients experience worsening of HRQOL still 5 years after surgery for oesophageal cancer.[12,13] Oesophageal cancer survivors usually no longer receive follow-up healthcare after 3 to 5 years of surgery. Yet, the pattern of longer-term recovery (beyond 5 years of surgery) in HRQOL is not known. It is, however, of great importance for patients, healthcare, and society to know the expected long-term recovery. Such knowledge could help the planning of the long-term needs of these patients. The aim of this study was to determine the HRQOL in 10 year-survivors of oesophageal cancer surgery.

Methods

Design

This prospective and population-based cohort study included 90% of all oesophageal cancer surgery patients in Sweden between April 1, 2001 and December 31, 2005. For the purpose of this study, patients were followed up for 10 years, and HRQOL data were obtained at 5 and 10 years following surgery. Patients' HRQOL measures at 10 years were compared with their HRQOL measures at 5 years, as well as the HRQOL measures of a reference population. Informed consent was obtained from all participants. The Regional Ethical Review Board in Stockholm, Sweden approved the study.

Data collection

A detailed description of this nationwide data collection can be found in other publications.[5,14] In brief, the study was based on a complete, nationwide network of 174 Swedish hospital departments with contact clinicians involved in diagnostic procedures or treatment of patients with oesophageal cancer. Information regarding patient and tumour characteristics, treatment, and complications were prospectively collected, and based on a predefined study protocol to ensure completeness and uniformity. Comorbidity was predefined as diabetes; cardiac, respiratory, renal or other specified conditions. By linking the unique personal identity number, assigned to all residents in Sweden, information about comorbidity was collected from the Swedish Patient Register, which contains all in-hospital diagnoses in Sweden since 1987 and all out-patient specialist care since 2001. Patients' self-reported HRQOL was collected by validated questionnaires at 6 months, 3, 5, and 10 years after surgery for oesophageal cancer. The cohort has been used for publications examining

HRQOL up to 5 years following surgery.[12,15,16] This is the first study using the cohort to examine HRQOL 10 years after surgery.

Health-related quality of life assessment

HRQOL was assessed using two self-administered questionnaires, both developed and validated by the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC).[17,18] The EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) consists of 30 items for measuring HRQOL aspects in cancer patients in general.[17] Questionnaire items are grouped into one global quality of life scale, five function scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea/vomiting, and pain), and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). An oesophageal cancer-specific questionnaire, the EORTC Quality of Life Questionnaire–OES18 (QLQ-OES18) was used to assess problems common among oesophageal cancer patients.[18] This 18-item questionnaire consists of four scales (dysphagia, reflux, eating difficulties, and oesophageal pain), and six single items (trouble swallowing saliva, choking, dry mouth, coughing, speech difficulties, and tasting problems). In both questionnaires, the four response alternatives were: “not at all”, “a little”, “quite a bit”, and “very much”. The only exception was the global quality of life scale, which had a seven-graded rating, ranging from 1 (“very poor”) to 7 (“excellent”).

Reference population

To obtain normative data for the QLQ-C30 and QLQ-OES18 questionnaires, a random sample of 6,969 adults in Sweden was invited to participate.[19] Among 4,910 (70.5%) participants, complete HRQOL data were obtained from 4,867 (99.1%) individuals. These data were used

as a proxy for baseline HRQOL, i.e., before the presentation of the cancer. Each patient in the operated cohort was individually matched by age (at HRQOL assessment), sex, and comorbidity (diabetes; cardiac, respiratory, renal or other specified conditions) to the reference population. This resulted in approximately 90 matched individuals (controls) from the reference population to each patient. This matching was done separately for the 5-year and 10-year assessment to avoid influence of older age and more comorbidity. Information about comorbidity was self-reported by the participants.

Statistical analysis

Questionnaire responses were linearly transformed into scores between 0-100, according to the scoring procedure in the EORTC manual.[20] In the global quality of life scale and the function scales, higher scores represent better HRQOL, whereas higher scores in symptom scales and individual items correspond to more symptoms. Missing items were handled as recommended in the EORTC scoring manual.[20] HRQOL measures were presented as mean scores with 95% confidence intervals (CIs). A difference of ≥10 mean scores between 5 and 10 years after surgery and between patients assessed at 10 years postoperatively and the reference population was defined as clinically relevant, since such mean score difference represents an appreciable difference in patients.[21] Therefore, statistical significance was only calculated for clinically relevant changes. Linear regression models were used to estimate mean score differences with 95% CIs between patients' HRQOL at 10 years after surgery and the reference population.

To investigate the extent of individual HRQOL changes between 5 and 10 years, compared to the reference population, we further categorized data into three groups: "improved",

"stable", or "deteriorated" for each HRQOL aspect. Thus, patients could be categorized as "deteriorated" in one function, but "improved" in a symptom, for example. "Improved" was defined as an increase of ≥10 mean scores in global quality of life and function scales, or a decrease of ≥10 mean scores in symptoms. "Deteriorated" represented a reduction of ≥10 mean scores in global quality of life or function scales, or an increase of ≥10 mean scores in symptoms. "Stable" defined a <10 mean score change between 5 and 10 years after surgery.

Statistical significance was analysed when the mean score differences were ≥10. Paired t-test was used for comparing mean scores at 5 years and 10 years and for comparison between patients who were categorized as improved, stable and deteriorated over time. Linear regression models were used when comparing patients' HRQOL at 10 years with the reference population's scores. P-values <0.01 were considered statistically significant.
The statistical software SAS 9.4 (SAS institute Inc., Cary, NC) was used for all statistical analyses, while STATA 12 for Windows (STATA Corp, College Station, TX, USA) was used for producing graphs.

Results

Patients

Among 616 patients included in the original cohort, 104 (17%) survived for at least 10 years. Among these, 92 (88%) responded to the HRQOL questionnaires at the 5 and 10 year follow-ups and were included in this study. Characteristics of included patients are presented in Table 1. Most patients were men, 71% were older than 70 years, and half hade one or more comorbidity .The dominating tumour type was adenocarcinoma of early pathological stage. A majority of patients underwent transthoracic surgery, 5% received neoadjuvant therapy and a third had postoperative complications.

HRQOL at 10 years compared to the reference population

Ten years after oesophageal cancer surgery, patients reported worse HRQOL scores in all 25 aspects compared to the reference population (Table 2, Figure 1 and 2). The mean score differences were clinically relevant and statistically significant for global quality of life, role function, social function, fatigue, nausea/vomiting, dyspnoea, insomnia, appetite loss, diarrhoea, dysphagia, reflux, eating difficulties, oesophageal pain, trouble swallowing saliva, choking, dry mouth, coughing, and taste problems. The most outstanding problems compared to the reference population were reflux (mean score difference: 34, 95% CI: 28 to 40; $p<0.0001$), eating difficulties (mean score difference: 27, 95% CI: 21 to 32; $p<0.0001$), diarrhoea (mean score difference: 24, 95% CI: 18 to 30; $p<0.0001$), and appetite loss (mean score difference: 22, 95% CI: 15 to 29; $p<0.0001$).

HRQOL changes between 5 and 10 years

On group level, there were no statistically or clinically relevant improvements in HRQOL between 5 and 10 years of surgery. Instead, the scores for 23 out of 25 aspects declined, while the scores representing financial difficulties and dysphagia remained the same (Table 2). Most of these mean score differences were not clinically relevant, but clinically relevant and statistically significant deteriorations were found for role function (mean score difference: -10, 95% CI: -16 to -5; p=0.0005) and appetite loss (mean score difference: -10, 95% CI: 4 to 16: p=0.0007).

HRQOL in patients who improved, were stable, and deteriorated between 5 and 10 years of surgery compared to HRQOL of the reference population

Improved: Even though no improvements in HRQOL could be seen on group level, 23-80% of patients improved between 5 and 10 years of surgery with HRQOL scores equivalent to what was reported by the reference population (Table 3). Reflux was the only aspect that became worse than the reference population both clinically and statistically significantly (mean score difference: 17, 95% CI: 8 to 26; p=0.0007).

Stable: In 7- 51% of patients who were stable in HRQOL between 5 and 10 years of surgery had clinically relevantly and statistically significantly worse scores than the reference population in all 25 HRQOL aspects (Table 3). The differences were particularly strong (>30 mean score difference) for role function (in 10% of patients), social function (11%), appetite loss (11%), constipation (8%), diarrhoea (22%), financial difficulties (7%), reflux (24%), trouble swallowing saliva (10%), choking (22%), speech difficulties (7%), and taste problems (10%)(Table 3).

Deteriorated: Among 12-47% of patients who deteriorated in HRQOL between 5 and 10 years of surgery had clinically relevantly and statistically significantly worse scores than the reference population in all 25 HRQOL aspects, and all mean score differences were >20 (Table 3). The most outstanding mean score differences (>40) were found for role function (in 38% of patients), nausea/vomiting (28%), dyspnoea (34%), insomnia (25%), appetite loss (32%), constipation (15%), diarrhoea (27%), financial difficulties (12%), reflux (39%), eating difficulties (35%), trouble swallowing saliva (16%), choking (18%), dry mouth (28%), coughing (29%), speech difficulties (14%), and taste problems (16%)(Table 3).

Discussion

This study shows that patients who have undergone surgery for oesophageal cancer 10 years earlier continue to deteriorate in HRQOL rather than recover. Their HRQOL is substantially worse that the reference population, with the most outstanding symptoms being reflux, eating difficulties, diarrhoea, and appetite loss.

Some methodological issues warrant consideration. A limitation is the lack of preoperative baseline HRQOL data. However, obtaining HRQOL data from a patient after receiving a diagnosis of oesophageal cancer and prior to extensive cancer surgery is misleading. These patients often suffer from psychological distress because of their awareness of their deadly cancer diagnosis and they usually suffer from severe disease symptoms, e.g. dysphagia and weight loss. To circumvent this issue, we used normative data from a matched and unselected reference population. These data simulate the patients' HRQOL, before the presentation of oesophageal cancer. The risk of selection bias was counteracted by the population-based study design with a high response rate. The fact that characteristic data for responders and non-responders were similar ($p<0.10$) also argues against selection bias. Information bias was counteracted by the use of well-validated questionnaires. The limited sample size in sub-group analyses may introduce a risk of chance influencing the results. Yet, all clinically relevant differences were clearly statistically significant, indicating sufficient precision. Oesophageal cancer is a disease that mostly affects older people. One might argue that deterioration in HRQOL was due to the normal ageing process or comorbidity. However, each patient was individually matched for age, sex and comorbidity with approximately 90 individuals (controls) from the reference population (n=4,910) in the comparisons at both 5 and 10 years following surgery, which should minimize any effects of age or comorbidity.

This is, to the best of our knowledge, the first prospective study of HRQOL up to 10 years after oesophageal cancer surgery. It is well established that oesophageal cancer surgery is associated with short-term and long-term deterioration in HRQOL.[8,22,23] It is worrying that the poor HRQOL after oesophageal cancer surgery is persistent over a 10-year period following the operation. This finding might, to at least some extent, be related to the surgical reconstruction of the upper gastrointestinal tract required for resecting an oesophageal cancer. The gastric cardia with its antireflux barrier is removed and the remaining part of the stomach is anastomosed to the proximal oesophagus in the chest or neck, which often causes severe problems with reflux and regurgitation as well as insomnia due to nightly reflux and regurgitation.[24,25] Despite the vagotomy needed to remove the oesophagus, the acidity of the gastric contents seem to be regained over time after surgery due to a vagal re-innervation, which probably explains the increased problems with reflux symptoms seen over time. Other anatomical issues might result from the fact that most of the gastric reservoir is removed by the construction of a thin gastric tube, which could contribute to eating difficulties and loss of appetite. Scarring and fibrosis of the proximal anastomosis might cause dysphagia. Furthermore, the vagotomy can result in dumping and problems emptying the stomach. The cumulative effect of these anatomical and physiological changes may result in a permanent reduction in HRQOL. In older patients who are not considered fit for surgery, an alternative treatment might be definite chemo-radiotherapy. This organ-sparing treatment might reduce the long-term consequences of surgery, although it does come with a risk of other complications and comorbidities. However, current scientific evidence does not support such approach in older patients considered fit enough to undergo

surgery because of a lower chance of long-term survival.[26] Nevertheless, a thorough discussion about the expected life situation after surgery with patients is encouraged.

In conclusion, it seems that long-term survivors of oesophageal cancer surgery experience reduced HRQOL in several aspects with persistent or even deterioration in specific symptoms. The HRQOL reduction appears to be not only related to older age, but also with the cancer and its treatment. Therefore, these findings call for the need for long-term follow-up including long-lasting rehabilitation plans for these patients.

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Conflict of interests

None declared.

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Table 1. Characteristics of 92 patients surviving 10 years of oesophageal cancer surgery and an age-, sex-, and comorbidity-matched reference population of 4,910 people.

Characteristics	Categorization	Patients	Reference population
		Number (%)	Number (%)
Total		92 (100)	4,910 (100)
Sex	Men	73 (79)	3,224 (66)
	Women	19 (21)	1,686 (34)
Age at operation (in years)	<40	0 (0)	0 (0)
	40-49	2 (2)	410 (8)
	50-59	6 (7)	1,073 (22)
	60-69	18 (20)	1,542 (31)
	70-79	39 (42)	1,903 (39)
	>79	27 (29)	0 (0)
Comorbidity	No	44 (48)	2,863 (58)
	Yes	48 (52)	2,047 (42)
Tumour histology	Squamous cell carcinoma	20 (22)	
	Adenocarcinoma	72 (78)	
Pathological tumour stage	0-I	49 (53)	
	II	29 (32)	
	III	13 (14)	
	IV	1 (1)	
Neoadjuvant treatment	No	87 (95)	
	Yes	5 (5)	
Surgical approach	Transthoracic	76 (83)	
	Transhiatal	14 (15)	
	Cervical	2 (2)	
Complications within 30 days of surgery	No	61 (66)	
	Yes	31 (34)	

Table 2. Health-related quality of life (HRQOL) 5 and 10 years after oesophageal cancer surgery for patients who survived at least 10 years (n=92), compared to an age-, sex-, and comorbidity-matched reference population (n=4,867).

HRQOL aspect	Mean scores (95% Confidence Intervals)			Mean differences (95% Confidence Intervals)			
	5 years after surgery	10 years after surgery	Reference population	5-10 years	p-value[1]	10 years to reference population	p- value[2]
EORTC QLQ-C30							
Global quality of life	70 (66 to 75)	66 (62 to 71)	76 (76 to 77)	4 (0 to 17)	-	-13 (-18 to -8)	<0.0001
Functional scales							
Physical	86 (82 to 89)	79 (74 to 83)	88 (87 to 88)	7 (4 to 13)	-	-9 (-13 to -5)	-
Role	84 (79 to 89)	74 (67 to 80)	88 (88 to 89)	10 (5 to 23)	0.0005	-15 (-22 to -9)	<0.0001
Emotional	84 (80 to 88)	80 (76 to 85)	86 (85 to 86)	4 (0 to 16)	-	-9 (-14 to -5)	-
Cognitive	84 (80 to 88)	78 (74 to 83)	88 (88 to 89)	6 (2 to 14)	-	-9 (-14 to -5)	-
Social	84 (80 to 89)	81 (76 to 86)	91 (91 to 92)	3 (-1 to 20)	-	-11 (-16 to -6)	<0.0001
Symptom scales							
Fatigue	29 (24 to 35)	37 (31 to 42)	19 (19 to 20)	-7 (-11 to 17)	-	19 (13 to 25)	<0.0001
Nausea/vomiting	14 (10 to 18)	18 (13 to 24)	3 (2 to 3)	-5 (-10 to 20)	-	16 (11 to 22)	<0.0001
Pain	17 (12 to 21)	21 (16 to 27)	19 (18 to 20)	-5 (-9 to 20)	-	6 (0 to 12)	-
Symptom items							
Dyspnoea	25 (20 to 31)	32 (26 to 39)	16 (16 to 17)	-7 (-12 to 23)	-	17 (10 to 24)	<0.0001
Insomnia	27 (21 to 33)	31 (24 to 38)	17 (17 to 18)	-4 (-10 to 24)	-	16 (9 to 22)	<0.0001
Appetite loss	15 (10 to 21)	25 (18 to 32)	3 (3 to 4)	-10 (-16 to 24)	0.0007	22 (15 to 29)	<0.0001
Constipation	10 (6 to 14)	12 (7 to 17)	5 (5 to 6)	-1 (-6 to 17)	-	6 (1 to 11)	-
Diarrhoea	28 (22 to 34)	29 (23 to 35)	6 (5 to 6)	-1 (-7 to 24)	-	24 (18 to 30)	<0.0001
Financial difficulties	11 (6 to 16)	11 (6 to 16)	4 (4 to 5)	-1 (-4 to 14)	-	8 (3 to 13)	-
EORTC QLQ-OES 18							
Disease-specific symptom scales							
Dysphagia	18 (13 to 23)	18 (13 to 24)	1 (1 to 1)	0 (-6 to 25)	-	18 (12 to 23)	<0.0001
Reflux	38 (31 to 44)	40 (24 to 45)	6 (6 to 7)	-2 (-8 to 26)	-	34 (28 to 40)	<0.0001
Eating difficulties	23 (18 to 28)	29 (24 to 34)	2 (2 to 3)	-6 (-11 to 19)	-	27 (21 to 32)	<0.0001
Oesophageal pain	22 (17 to 27)	19 (15 to 24)	4 (4 to 5)	3 (-1 to 17)	-	16 (11 to 20)	<0.0001

Disease-specific items							
Trouble swallowing saliva	12 (7 to 17)	15 (10 to 21)	1 (1 to 1)	-4 (-10 to 25)	-	14 (9 to 20)	<0.0001
Choking	16 (11 to 21)	20 (14 to 25)	4 (3 to 4)	-3 (-10 to 26)	-	17 (11 to 22)	<0.0001
Dry mouth	23 (18 to 29)	28 (22 to 34)	11 (11 to 12)	-4 (-10 to 26)	-	16 (10 to 22)	<0.0001
Coughing	22 (16 to 28)	26 (20 to 33)	13 (13 to 14)	-5 (-12 to 29)	-	13 (6 to 19)	0.0002
Speech difficulties	7 (3 to 10)	10 (6 to 15)	2 (2 to 2)	-4 (-7 to 16)	-	8 (3 to 13)	-
Taste problems	13 (8 to 18)	14 (9 to 19)	2 (1 to 2)	-1 (-6 to 21)	-	13 (7 to 18)	<0.0001

Where mean scores differed clinically relevantly by ≥10 points, paired t-test[1] or linear regression[2] was used to test for statistical significance.

Table 3. Health-related quality of life (HRQOL) changes categorized as improved, stable and deteriorated between 5 years and 10 years in 92 long-term oesophageal cancer survivors compared with an age-, sex-, and comorbidity-matched reference population of 4,847 randomly selected people presented as mean score differences (MSD) and 95% confidence intervals (CIs).

HRQOL aspect	Mean scores in patients who improved, were stable and deteriorated between 5 and 10 years of surgery compared to the mean scores of the reference population								
	Improved			Stable			Deteriorated		
	Number (%)	MSD (95% CI)	p-value	Number (%)	MSD (95% CI)	p-value	Number (%)	MSD (95% CI)	p-value
EORTC QLQ-C30									
Global quality of life	21 (23)	4 (-5 to 12)	-	47 (51)	-13 (-20 to -7)	<0.0001	24 (26)	-27 (-35 to -18)	<0.0001
Functional scales									
Physical	28 (30)	9 (5 to 14)	-	33 (36)	-14 (-20 to -8)	<0.0001	31 (34)	-21 (-28 to -13)	<0.0001
Role	47 (51)	8 (5 to 12)	-	9 (10)	-36 (-57 to -15)	0.0044	35 (38)	-42 (-51 to -32)	<0.0001
Emotional	40 (43)	5 (0 to 10)	-	26 (28)	-17 (-26 to -9)	0.0004	26 (28)	-23 (-29 to -17)	<0.0001
Cognitive	36 (39)	7 (3 to 12)	-	21 (23)	-15 (-22 to -8)	0.0003	35 (38)	-23 (-30 to -16)	<0.0001
Social	53 (58)	3 (-1 to 7)	-	10 (11)	-34 (-50 to -18)	0.0009	28 (30)	-30 (-38 to -22)	<0.0001
Symptom scales									
Fatigue	24 (26)	0 (-10 to 10)	-	25 (27)	12 (5 to 20)	0.0026	43 (47)	33 (25 to 42)	<0.0001
Nausea/vomiting	56 (61)	2 (-1 to 5)	-	10 (11)	24 (11 to 37)	0.0022	26 (28)	44 (34 to 54)	<0.0001
Pain	51 (55)	-9 (-15 to -4)	-	14 (15)	11 (-1 to 22)	0.0703	27 (29)	32 (21 to 43)	<0.0001
Symptom items									
Dyspnoea	39 (42)	-10 (-16 to -5)	0.0005	22 (24)	24 (19 to 29)	<0.0001	31 (34)	45 (33 to 57)	<0.0001
Insomnia	43 (47)	-11 (-15 to -8)	<0.0001	26 (28)	27 (20 to 33)	<0.0001	23 (25)	53 (41 to 65)	<0.0001
Appetite loss	53 (58)	-2 (-3 to -2)	-	10 (11)	33 (25 to 41)	<0.0001	29 (32)	62 (49 to 75)	<0.0001
Constipation	71 (77)	-5 (-6 to -5)	-	7 (8)	42 (24 to 60)	0.0013	14 (15)	46 (32 to 60)	<0.0001
Diarrhoea	46 (50)	3 (-2 to 7)	-	20 (22)	37 (29 to 44)	<0.0001	25 (27)	53 (42 to 65)	<0.0001
Financial difficulties	74 (80)	-1 (-3 to 1)	-	6 (7)	37 (24 to 50)	0.0007	11 (12)	56 (37 to 75)	<0.0001
EORTC QLQ-OES 18									
Disease-specific symptom scales									
Dysphagia	52 (57)	4 (1 to 8)	-	14 (15)	29 (20 to 39)	<0.0001	25 (27)	39 (26 to 52)	<0.0001
Reflux	33 (36)	17 (8 to 26)	0.0007	22 (24)	39 (30 to 48)	<0.0001	36 (39)	46 (36 to 55)	<0.0001
Eating difficulties	26 (28)	9 (2 to 16)	-	34 (37)	21 (15 to 28)	<0.0001	32 (35)	47 (38 to 55)	<0.0001
Oesophageal pain	56 (61)	6 (2 to 11)	-	10 (11)	13 (5 to 20)	0.0039	26 (28)	37 (28 to 46)	<0.0001
Disease-specific items									

Trouble swallowing saliva	67 (73)	2 (-1 to 4)	-	9 (10)	32 (31 to 33)	<0.0001	15 (16)	61 (46 to 76)	<0.0001
Choking	50 (54)	-2 (-4 to -1)	-	20 (22)	35 (30 to 41)	<0.0001	19 (18)	48 (35 to 60)	<0.0001
Dry mouth	42 (46)	-8 (-12 to -4)	-	24 (26)	27 (20 to 33)	<0.0001	26 (28)	46 (35 to 56)	<0.0001
Coughing	50 (54)	-8 (-13 to -4)	-	13 (14)	28 (18 to 37)	<0.0001	27 (29)	45 (35 to 56)	<0.0001
Speech difficulties	73 (79)	-2 (-3 to -1)	-	6 (7)	37 (23 to 52)	0.001	13 (14)	49 (34 to 64)	<0.0001
Taste problems	67 (73)	0 (-2 to 1)	-	9 (10)	39 (28 to 51)	<0.0001	15 (16)	54 (41 to 69)	<0.0001

Improved mean scores were defined by an increase over time of ≥10 mean scores in global quality of life and function scales, or a reduction of ≥10 mean scores in symptoms. Deteriorated mean scores were defined as a reduction of ≥10 mean scores over time in global quality or function scales, or an increase of ≥10 mean scores in a symptom severity scale. Stable mean scores were defined as less change than 10 means scores over time. Where mean scores differed clinically relevantly by ≥10 points paired t-test was used to test for statistical significance. P <0.01 was considered statistically significant.